Impaired function of macrophage Fc gamma receptors in end-stage renal disease.
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Patients with severely impaired kidney function as a result of the final stages of kidney disease often undergo hemodialysis, a procedure whereby the patient's blood is shunted from the body, cleansed of impurities in a machine, and returned to the body. A common complication of hemodialysis is a high infection rate, the primary cause of death among these patients. The reason for this high rate is not known, but it is likely that the patients' immune systems are not functioning adequately. A type of white blood cell normally active in the immune response, the macrophage, was studied in 56 dialysis patients and 20 healthy control subjects. One way macrophages fight invading microorganisms such as bacteria is by engulfing and eliminating them after the bacteria have been coated with antibodies. Macrophages can do this because they possess molecules on their surfaces (Fc receptors) that can recognize and bind to the tail regions (Fc region) of antibodies. The competence of the patients' macrophages was tested in two ways: by measuring the cells' ability to remove antibody-coated red blood cells that had been injected into the patients' bloodstream (clearance test), and by measuring their ability to bind to these same cells under laboratory conditions. In the patients, one type of Fc receptor (the Fc-gamma receptor, which binds to antibodies of the IgG-class) was clearly impaired in both test conditions as compared with the control group. Macrophage binding to antibody-coated red blood cells under laboratory conditions showed partial improvement after hemodialysis. Nine of the 56 patients experienced severe infections during the two-year follow-up period. This subgroup had even greater impairment of Fc-receptor function in the clearance studies than that shown by the remaining 47 patients. It is likely that this abnormality in Fc receptor function among patients with end-stage renal disease undergoing dialysis contributes to their high rate of infection. (Consumer Summary produced by Reliance Medical Information, Inc.)

Captions: Macrophage clearance of red cells. (graph); Recognition of Human IgG-coated red cells. (graph); Clearance in patients with circulating immune complexes. (graph)

Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age. (From the Collaborative Project on Preterm and Small for Gestational Age Infants /POPS, in the Netherlands)

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Infants born prior to week 32 of gestation are called very preterm, and infants weighing less than 1,500 grams (about 3.3 pounds) are called very-low birthweight. To tabulate the outcome of such pregnancies, a total of 1,338 live births before week 32 and under 3.3 lbs. were followed for a period of five years. During that period, 372 children died, leaving 966. Of these, 39 were lost to follow-up. A total of 927 children were therefore examined for impairment, disability, or handicap. In the present study, impairment is defined as any abnormality that does not lead to disability. A disability involves some loss of function, whereas a handicap is a disability that results in a social disadvantage. A total of 257 children had some sort of disability or handicap, often more than one. Behavioral disturbances were common, and were not limited to the children with disabilities. Eighteen of the 209 children (8.6 percent) who were otherwise normal had behavioral disturbances, as did 13.7 percent of the children with impairments, 33.3 percent of the children with disabilities, and 49.3 percent of the handicapped children. There was some respiratory impairment in 249 children, but the respiratory system was not a common cause of disability. More commonly, serious disability and handicap resulted from abnormal language and speech development, mental development, and nerve and muscle function. The status of 10 percent of the children had improved when compared with an examination conducted at two years of age, while the status of 7 percent had worsened. While the disability rate is high among the children in this study, the results nevertheless indicate that a large majority of children born very preterm or of very low birth weight survive without serious disability or handicap. (Consumer Summary produced by Reliance Medical Information, Inc.)

In 1983, the Project On Preterm and Small for gestational age infants (POPS) was started to investigate the relation between prenatal/perinatal factors and mortality/morbidity in very preterm and very-low-birthweight (VLBW) infants. The obstetric and paediatric features of the study population with respect to pregnancy, delivery, birth, and hospital stay after birth have been published elsewhere, [1-8] as well as the results of the follow-up study until the corrected age of two years. [9-17] Because not all sequelae can be diagnosed yet at that age, [18] the same cohort of children was reassessed in 1988 at a chronological age of five years.

We here report the overall outcome of the assessment at five years of age according to the International Classification of Impairments, Disabilities, and Handicaps of the World Health Organisation (WHO). [19]

Patients and methods

Of the original study population (1338 liveborn infants delivered in the Netherlands between Jan 1 and Dec 31, 1983, before thirty-two completed weeks of gestation and/or with a birthweight of less than 1500 g), [12] 372 children had died before the age of five. The 966 surviving children were enrolled in the five-year follow-up programme.

The areas and methods of assessment were as follows:

Examination Assessment

Congenital malformation Physical examination

Neuromotor function Neurological assessment

Motor developmental assessment

Mental development Social and adaptation section,

Denver developmental screening

test

Hearing Audiometry, otoscopy

Visual function Spontaneous eye movements, lens

opacity, cover test, visual fields,

Titmus test, Landolt-C acuity test

Language and speech Standardised Dutch test

development

Musculoskeletal system Physical examination

Respiratory tract Questionnaire

Ear nose throat disorders Questionnaire

Behaviour Questionnaire, opinion of parents

and/or paediatrician

Growth Height, weight, head circumference

A detailed description of the tests and examinations is available on request. The overall outcome includes the results for eight areas of assessment (behaviour and growth were not taken into account because unequivocal interpretation of outcome data based on the WHO classification of impairments, disabilities, and handicaps is virtually impossible).

Data were processed with the 'SPSS-X' (SPSS Inc, Chicago, Illinois, USA) and 'SAS' (SAS Institute, Cary, North Carolina, USA) programs.

In each area, a child was categorised as either impaired, disabled, or handicapped, according to the

following WHO definitions. [19] "An impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. A disability is any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered

[TABULAR DATA OMITTED]

normal for a human being. A handicap is a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual." Impairment is disturbance at organ level; disability is the consequence of impairment for function and activity; and handicap is the social disadvantage experienced by the individual as a result of the disability. A child was regarded as impaired in the overall outcome if he or she had impairment in an area of examination that did not lead to any disability. A child was regarded as disabled in the overall outcome if he or she had a disability on an area of examination or if a multiplicity of impairments caused loss of function or activity. A child was regarded as handicapped if he or she had a handicap in an area of examination or if multiplicity of disabilities caused a social disadvantage. All children who needed special education were regarded as handicapped. A handicap was considered minor if it did not seriously interfere with everyday life and did not require extensive caretaking; and major when it did interfere with everyday life and when it led to a life of dependency or institutionalisation. In cases of doubt, the child was allocated to the more severe group to avoid understimation. Behavioural disturbances will only be mentioned here according to the patient's opinion and the investigator's impression based on excessive mood swings, impulsivity, restlessness, or limited concentration span, and social and emotional development disorders.

Results

At five years of age, 39 out of 966 survivors were lost to follow-up. Thus, 927 (96%) children had a formal assessment. The overall outcome as a percentage of liveborn as well as of assessed children is shown in table I. The percentage of impairments, disabilities, and handicaps in the subgroups are similar to those in the total cohort. Table II shows the outcome for each of the eight areas of assessment. The highest handicap frequencies were found in neuromotor function, mental development, and language and speech development. The disabilities ranged from 0.2 to 13% and the impairments from 4 to 26%. Behavioural disturbances were present in 188 children (20%) and special education had been obtained for 108 (12%).

The 257 disabled children (including the 134 with handicap) often had more than one disability (table III); disorders of neuromotor function, mental development, and/or language and speech development were often found in the same child. 20.3% (188/927) of the children had behavioural disturbances--8.6% (18/209) were normal, 13.7% (63/461) impaired, 33.3% (41/123) disabled, and 49.3% (66/134) handicapped. Compared with the results of the follow-up study done at two years in 916 children, there was a lower rate of minor handicap and a similar rate of

[TABULAR DATA OMITTED]

TABLE IV--OVERALL HANDICAP AT TWO YEARS CORRECTED AGE AND AT FIVE YEARS CHRONOLOGICAL AGE

Outcome at two yr Outcome at five yr

% % % %

assessed liveborn assessed liveborn

Handicap No (n=944) (n=1338) (n=927) (n=1338)

None 774 81.9 57.8 793 85.5 59.2

Minor 111 11.8 8.3 73 7.9 5.5

Major 59 6.3 4.4 61 6.6 4.6

major handicap (table IV). However, many children had shifted from one subgroup to another; a more favourable outcome was seen in 10%, and a less favourable outcome in 7% of the children. Such a shift was mainly due to a change in severity within the same area, especially in neuromotor function.

The relation between outcome and gestational age was analysed in the 648 assessed children with a gestational age of less than thirty-two weeks, including all birthweights (fig 1). A systematic decrease of handicaps and disabilities was found with increasing gestational age (odds ratio 0.86 per week gestation, $p = 0.04$ for handicap; odds ratio 0.86, $p = 0.008$ for disabilities including handicap). Inclusion of birthweight in a multivariate model (logistic regression analysis) did not change the relation with gestational age, and birthweight itself was not associated with outcome.

Discussion

Standardisation is essential in long-term follow-up surveys, both to minimise bias and to optimise the comparability of outcome. We adhered to the International Classification of the WHO as strictly as possible. Although this classification is designed for adults, some subject areas such as orientation and mobility can be applied to a five-year-old child, and physical independence and social integration can be used to some extent. Occupation and economic self-sufficiency could not of course be taken into account.

We have shown that most very preterm and VLBW infants born in 1983 in the Netherlands survived to the age of five years without handicap. Fig 2 compares our results with those of other geographically defined studies on VLBW infants. [20-24] However, these surveys are not strictly comparable because of, among other things, differences in intake criteria, sample size, duration of follow-up, and outcome definitions. [25] Nonetheless, our findings seem to point to a decrease in mortality without an increase in handicap for liveborn infants, and thus a decrease in total adverse outcome. Comparison with a formal control group has not yet been possible owing to the costs of such a study. Comparison with the general Dutch population (data from the Dutch Continuous Health Enquiry, Central Bureau of Statistics) [26] shows that 17% of all Dutch children aged from five to fourteen years have some "physical" disability, of which 4% have severe disabilities that cause handicap (mental disorders and institutionalised children excluded). Adjusting for the same criteria, we found that 23% of the children in our study were physically disabled; these included the 13% who were handicapped. Thus, in relation to the small number of cases involved, the contribution of very preterm and VLBW infants to the total number of disabled and handicapped children is very low. [27]

We found impairments in half the children. Provided that such impairments do not cause disability or handicap, they seem to be of limited importance. Moreover, in a small reference group of 52 children attending normal schools and undergoing the same extensive assessment by the same paediatricians the impairment rate was as high as 52%. Therefore, as an outcome measure for follow-up studies of very preterm infants, the term impairment according to WHO definitions seems to be of limited value. The

significant association between gestational age and outcome was detected by an analysis that included only children with a gestational age of less than thirty-two weeks. The older infants in the study group had had a birthweight of less than 1500 g (admission criterion to the study). To prevent selection bias, data from these children were omitted from the analysis.

In contrast to the studies reviewed by Ehrenhaft et al [28] we found no association with birthweight. However, in those studies birthweight was used to define study populations, which led to a non-homogeneous gestational age distribution. [29] Most children with abnormal overall outcome had a combination of neuromotor function disorder, mental retardation, and language and speech abnormality. In VLBW infants in the Oxford Region Register, 52% had a combination of cerebral palsy and intellectual impairment, [30] and in Sweden mental retardation seemed often to accompany cerebral palsy in children of all birthweights. [31] We did not exclude children with congenital malformations from the study because these children are an intrinsic part of such a population. They account for handicaps, disabilities, and impairments that clearly are of antenatal origin.

Although the major handicap frequencies at two and five years of age were similar, these data do not refere to the same children; such a "shift" has also been found by other investigators. [32,33] These changes in outcome at different ages might be due to development of the child or because the testing of certain abilities is easier at an older age--eg, language and speech development, [33] family status, [34] or a combination of these factors. Many learning and behavioural difficulties can be detected only at an even older age. [18,32,35] Therefore, we are planning to do a reassessment at nine years, in which we shall focus on cognitive functions, educational achievement, and behaviour in relation to neurological maturation.

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Captions: Impairment, disability, and handicap in study population. (table); Abnormal outcome in assessed children. (table); Overall disability and multiple disabilities. (table); Overall handicap and two and five years. (table); Relation between outcome and gestational age. (graph); Comparison of studies of VLBW infants. (graph)

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